REMARKS

The present invention relates to methods of treating a disease mediated by abnormal expression of REMODELIN in a human. Claims 23-24 are pending and under consideration in the present application. Claims 1-22 and 25-55 were withdrawn without prejudice to the inclusion of the subject matter of these claims in any later filed application(s) in a Response to Restriction Requirement filed on July 23, 2004.

Rejection of claims 23-24 pursuant to 35 U.S.C. §112, second paragraph

The Examiner has rejected claims 23-24 under 35 U.S.C. §112, second paragraph, for being indefinite. The Examiner states that claim 23 depends from claim 19, which depends from claim 13, which depends from claim 1, and such claims have been withdrawn from consideration. The Examiner contends that since the claims from which claim 23 depends are not under examination, it is impossible to know the metes and bounds of the claims presently under consideration.

Applicants appreciate the Examiner's interpretation of claim 23 in order to facilitate examination and prosecution of this application. However, Applicants have amended claim 23 to incorporate subject matter from the claims from which it depends and to recite subject matter different from the interpretation the Examiner afforded claim 23 and 24. Applicants respectfully submit that the present amendment to claim 23 overcomes the Examiner's rejection of claim 23 and 24 pursuant to 35 U.S.C. §112, second paragraph, and further overcomes the Examiner's rejections as set forth below.

Reconsideration and withdrawal of the rejection to claims 23 and 24 under 35 U.S.C. §112, second paragraph, is respectfully requested at this time.

Rejection of claims 23-24 pursuant to 35 U.S.C. §112, first paragraph

The Examiner has rejected claims 23-24 under 35 U.S.C. §112, first paragraph, for lack of written description. The Examiner is of the opinion that the specification fails to provide adequate written description for the claimed invention. The Examiner asserts that an antisense sequence directed towards the nucleic acid that encodes REMODELIN is a broad genus, and an adequate number of representative species is not disclosed to demonstrate possession of this genus.

Applicants respectfully submit that the genus presently claimed is not as broad as the Examiner asserts. Rather, Applicants have amended claim 23 to recite an isolated nucleic acid complementary to human REMODELIN (SEQ ID NO:3), and therefore, it is the only species necessary to represent the presently claimed invention. Applicants have demonstrated possession of human REMODELIN, as evidenced by the sequence listing filed with the present application. Further, the parent application of the present application, now U.S. Patent 6,630,325 sets forth a nucleic acid complementary to SEQ ID NO:3 in claim 8. Therefore, the United States Patent Office has already determined that the specification provides adequate written description for a nucleic acid complementary to SEQ ID NO:3.

The Examiner argues that although there are examples of using antisense REMODELIN sequences in the specification as filed, there is no description of how to identify an antisense sequence to REMODELIN that would inhibit REMODELIN expression. The Examiner also argues that the specification as filed provides no description of how to administer an oligonucleotide to a human such that the oligonucleotide would reach the affected cells and inhibit REMODELIN, thus treating a disease such as hypertrophic scar formation.

Applicants submit that the specification as filed provides ample description as to how to identify an antisense sequence to REMODELIN. As set forth in the claims as presently amended, the antisense nucleic acid of the present invention is complementary to SEQ ID NO:3. The skilled artisan, provided with the written description in the specification can readily identify an antisense nucleic acid complementary to SEQ ID NO:3. Further, the specification provides more than adequate description of how to formulate and administer a pharmaceutical composition, such as a REMODELIN antisense nucleic acid. Specifically, at page 92, beginning at line 19, buffers such as HEPES that are used in the administration of an antisense molecule to a mammal, such as a human are described. Beginning at line 12 on page 93, various routes of administering a pharmaceutical composition comprising an antisense REMODELIN nucleic acid are described. At page 141, beginning at line 6, the specification provides description regarding how to transfect mammalian cells with a vector comprising antisense REMODELIN. Thus, the specification provides not only adequate written description, but actual working examples of how to administer an antisense REMODELIN nucleic acid.

The Examiner cites Branch (1998, TIBS 23: 45-50) as teaching that it is difficult to predict what portions of an RNA molecule will be accessible *in vivo* and that it empirical

screening of a large number of candidate oligonucleotides is required to identify effective antisense molecules. The Examiner asserts that the specification teaches one example of an antisense REMODELIN nucleic acid, but does not provide adequate written description for the entire genus of antisense nucleic acid capable of inhibiting REMODELIN gene expression.

Applicants submit, as set forth above, that the specification provides adequate written description for an antisense nucleic acid that is complementary to human REMODELIN (SEQ ID NO:3), and therefore, written description for an entire genus of antisense nucleic acids is not necessary because it is not presently claimed. Further, Applicants provide the empirical data discussed in Branch. Specifically, Applicants demonstrate that an antisense REMODELIN nucleic acid administered to mammalian cells results in morphology changes and increased turnover. *See* page 141, beginning at line 6. Given the description present in Applicants' specification, empirical screening of large sample of antisense nucleic acids is not necessary, nor is it necessary to determine which portions of the REMODELIN RNA are accessible to an antisense nucleic acid because Applicants provide the written description to accomplish the methods of the present invention.

For the reasons state above and the amendments to the claims under consideration, Applicants respectfully submit that the Examiner's rejection of claim 23-24 under 35 U.S.C. §112, first paragraph, for lack of written description, should be reconsidered and withdrawn.

Rejection of claims 23-24 under 35 U.S.C. §112, first paragraph

The Examiner has rejected claims 23-24 pursuant to 35 U.S.C. §112, first paragraph, for lack of enablement. The Examiner asserts that methods of gene therapy directed towards inhibiting gene expression in humans are not enabled because the art is unpredictable. The Examiner asserts that delivering genes *in vivo* is not routine in the art because of delivery, specificity and duration problems. The Examiner cites Agrawal et al. (2000, Molecular Medicine Today 6: 72-81), Branch, Opalinska et al. (2002, Nature Review, 1: 503-514) and Jen et al. (2000, Stem Cells 18: 307-319) to purportedly demonstrate that the therapeutic application of nucleic acids *in vivo* is hindered by delivery problems, target accessibility and potential unpredictable effects. The Examiner also asserts that oral, intraocular and topical administration of antisense nucleic acids is not routine in the art. The Examiner argues that in order to use an antisense REMODELIN nucleic acid in the methods of the present invention, the skilled artisan

would have to empirically determine one of a variety of variables, and such determination would constitute undue experimentation.

The Examiner sets forth the criteria enunciated in *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988) and later reproduced at MPEP 2164.01(a) as the criteria used for determining whether undue experimentation is necessary in order to practice the method of the present invention. The Examiner does not mention the other pillar of the current law regarding enablement, even though it bears equal consideration as the *Wands* factors, and that is "A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); MPEP 2164.01. Further, and most pertinent to the Examiner's rejections, the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *see* MPEP 2164.01.

The references cited by the Examiner demonstrate that the art typically engages in the type of experimentation the Examiner cites as undue, and therefore such experimentation is not undue. In addition, the references cited by the Examiner do not characterize antisense therapy in such a negative light. Opalinska et al. refer to delivery problems as "easily addressed" (page 507, second column), and Table 1 on page 508 provides an extensive list of at least ten separate studies in which malignant, inflammatory, cardiac and infectious diseases were treated with nucleic acid-based therapies. Jen et al. state that "targeting mRNA is attractive because mRNA is more accessible than the corresponding gene" (abstract), thus addressing the Examiner's concerns regarding accessibility of targets. Jen et al. further teaches the range of delivery vehicles that have been used to deliver antisense nucleic acids to cells (page 313, second column), demonstrating that the art typically engages in experimentation regarding delivery of antisense nucleic acids. Agrawal et al. characterize antisense nucleic acids as "simple and efficient" (see abstract) and provides fifteen examples of clinical trials employing antisense oligonucleotides to treat various diseases. Agrawal et al. further provides sequences and a significant amount of guidance in the optimal design of antisense nucleic acids (pages 76-80). Branch states, "there is growing evidence that antisense molecules can be useful pharmaceutical tools when applied carefully" (page 50, first column), and indicates that the use of antisense

technologies "must be explored on a case-by-case basis" clearly indicating that the art is accustomed to experimenting with antisense technology in order to use it. Therefore, the Examiner has provided a survey of the skill in the art and the level of experimentation typical therein. The references cited demonstrate that the level of experimentation necessary to use antisense therapies is not undue, but rather commonplace for those of skill in the art.
The Examiner has ignored the fact that antisense technologies are not only used to treat various serious and life-threatening diseases, but that the Food and Drug Administration approved an antisense therapy for treatment of cytomegalovirus-induced retinitis sold under the brand name of Vitravene and referred to in Opalinska et al. at page 507. Vitravene was approved by the FDA in August of 1998 and is administered via intraocular injection, negating the Examiner's statement that such administration routes were not routine in the art at the time of filing. More importantly, Vitravene is approved by the FDA, which demands substantial evidence demonstrating safety and efficacy of a drug prior to approval. *See* 21 U.S.C. §355(b). Thus, despite the Examiner's various contentions, the art and the FDA do not view antisense therapies as unpredictable, but rather as effective treatments for various diseases.

The Examiner also argues that the skilled artisan would have to determine the sequence to use in order to inhibit REMODELIN expression with an antisense molecule. As discussed above, Applicants have amended claim 23 to recite an antisense nucleic acid complementary to human REMODELIN (SEQ ID NO:3), and have provided data for determining which portion of an antisense REMODELIN nucleic acid can cause morphologic and cell turnover changes in a cell expressing REMODELIN. Therefore, the skilled artisan, equipped with the knowledge in the art as demonstrated by Opalinska et al, Jen et al., Branch, Agrawal et al. and the specification as filed, is enabled to use an antisense REMODELIN nucleic acid in the methods of the present invention.

For the reasons set forth above, Applicants respectfully request reconsideration and withdrawal of the Examiner's rejection of claims 23-24 pursuant to 35 U.S.C. §112, first paragraph.

Summary

Applicants respectfully submit that each rejection of the Examiner to the claims of the present application has been overcome, and that claims 23-24 are now in condition for allowance. Applicants further submit that no new matter has been added by way of the present amendment. Reconsideration and allowance of these claims is respectfully requested at the earliest possible date.

Respectfully submitted,
Volkhard Lindner *et al.*

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(Date)

By: _____

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